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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,721	10/20/2005	Alan Barge	056291-5207	5602

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EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
4161	

MAIL DATE	DELIVERY MODE
05/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,721	BARGE, ALAN	
	Examiner	Art Unit	
	PAUL ZAREK	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/30/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-13* is/are pending in the application.

4a) Of the above claim(s) *13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/12/2005, 10/20/2005, 04/30/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

7. Claims 1-10 have been canceled by the Applicant. Claim 11-13 were added on 04/30/2008 per response to Examiner's request for Restriction and species election. Claims 11-13 are currently pending. This is the first Office Action on the merits of the claim(s).

8. Applicant's election of Group II and the species, (4-(2-cholor-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline), in the reply filed on 04/30/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

9. Claim 13 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/30/2008.

Priority

10. Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) based on an application filed in the United Kingdom on 11/13/2002.

Formalities

11. The information disclosure statement filed 5/12/2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the foreign patent document, WO 02/057271 A1, was not supplied by Applicant. The non-patent literature documents,

Michael, et al. and Hiromichi, et al., were not supplied by Applicant. The information disclosure statement filed on 10/20/2005 also fails to comply with 37 CFR 1.97, 1.98 and MPEP § 609. The foreign patent document, WO 04/041829, was not supplied by Applicant. They have been placed in the application file, but the information referred to therein that has been lined through has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 11 and 12 are directed toward a method for the "prophylaxis" of pancreatic cancer. The Applicant does not provide a definition of "prophylaxis" in the

Specification. The Examiner understands "prophylaxis," defined by Stedman's Medical Dictionary 27th Ed., as the "[p]revention of disease or of a process that can lead to a disease." In the Instant Application, "disease" is taken to mean "pancreatic cancer." The current state of the art teaches that pancreatic cancer prophylaxis, if possible, is attainable primarily through dietary modifications. "Protection is mainly provided by fruits, vegetables, and vitamins." (Sarker et al, pg 330, 2nd paragraph from bottom) Doucas, et al., mention only the possible advantages of COX inhibitors and NSAIDs as pharmacologic interventions for the prevention of pancreatic cancer (pgs 433-436). The Applicant does not supply data indicating that treating patients with the claimed pharmaceutical composition would prevent the onset or induction of pancreatic cancer. The data supplied describe only the treatment models of pancreatic cancer, not prevention models.

8. In the Instant Application, the Applicant claims a treatment method comprising a "synergistically effective therapeutic amount" of a Src inhibitor (4-(2-cholor-5-methoxyanilino)-6-methoxy-7-(*N*-methylpiperidin-4-ylmethoxy)quinazoline) and gemcitabine. In the Specification the Applicant defines "synergism" to be present "if the conventional dose of the Src inhibitor or gemcitabine may be reduced without detriment to one of more of the extent of the response, response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used." (pg 21, lines 16-20) The Specification defines a preferred dose of a Src inhibitor and gemcitabine (pg 23, lines 16-24 and 25-31, respectively. However, the Applicant does not disclose how or whether the invention as claimed alters

these described doses. Further, the increased anti-tumor effect of Src-1 and gemcitabine in the example on pages 28-29 can be reasonably described as "additive" rather than "synergistic."

9. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (MPEP § 2164.01(a))

A. The breadth of the claim: the claims are drawn to a method of treating *or preventing* pancreatic cancer by administering a *synergistically* effective dose of a Src inhibitor and gemcitabine;

B. Nature of the invention: a method of treating or preventing pancreatic cancer by administering a synergistically effective dose of a Src inhibitor and gemcitabine;

C. The state of the prior art: both Src inhibitors and gemcitabine have been used to treat tumors, including pancreatic cancer, but not to prevent tumors. Prevention of pancreatic cancer is not achievable through drug treatment;

D. Level of one of ordinary skill in the art: physicians and scientists;

E. Level of predictability in the art: pharmacologic inhibition of the EGF-R pathway along in combination with gemcitabine is an effective treatment for cancers in general, and pancreatic cancer in particular;

F. Amount of direction provided by the inventor: Applicant discloses support for treating a murine model of pancreatic cancer with the elected

Src inhibitor and gemcitabine, but the effects appear additive rather than synergistic;

G. Existence of working examples: Applicant provides data showing an increased anti-tumor effect from combined Src-inhibition and gemcitabine treatment over treatment by either agent alone; and,

H. Quantity or experimentation needed to make or use the invention based on the content of the disclosure: prophylaxis of pancreatic cancer through pharmacologic means has remained elusive to this day. Applicant has provided no support that Src inhibition coupled with gemcitabine treatment would an effective regimen to prevent the occurrence of pancreatic cancer. Moreover, the data supplied by the Applicant demonstrates an additive, rather than synergistic, effect when combining the elected Src inhibitor with gemcitabine to treat pancreatic cancer.

10. Undue experimentation would be required to use the invention as claimed.

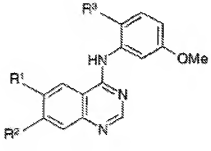
Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 11 and 12 rejected under 35 U.S.C. 103(a) as being unpatentable over Hennequin, et al., (International Patent Application WO02/092577) in view of Lutz, et al. (Biochem. and Biophys. Res. Comm.) and Bruns et al (Cancer Res., 06/2001).

13. Claims 11 and 12 of the Instant Application are directed to a method of treating or preventing pancreatic cancer with a pharmaceutical composition comprising the Src-inhibitor, 4-(2-cholor-5-methoxyanilino)-6-methoxy-7-(*N*-methylpiperidin-4-ylmethoxy)quinazoline, and gemcitabine, a commonly used nucleoside analog used in



chemotherapy. Hennequin, et al., teach the "use of a quinazoline derivative for the formula I . . . for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease." (Claim 9) The compound claimed in the Instant Application is a specific species of the Formula I. Further, Hennequin, et al., specifically claim 4-(2-cholor-5-methoxyanilino)-6-methoxy-7-(*N*-methylpiperidin-4-ylmethoxy)quinazoline, and describe that it is capable of inhibiting Src. (Claim 5, 1st compound) Hannequin, et al, disclose "it is believed that the compounds of the present invention provide an anti-tumor effect by way of inhibition of the Src family of non-receptor tyrosine kinases, for example, by inhibition of one or more of c-Src, c-Yes and c-Fyn" (pg 3, lines 30-33). The inventors go on to state, "Generally, the compounds of the present invention possess potent inhibitory activity against the Src family of non-receptor tyrosine kinases, for example by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory ativity (sic) against other tyrosine kinase enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase" (pg 4,

lines 15-19) While Hennequin, et al., do not explicitly mention pancreatic cancer, Lutz, et al., teach that Src is activated in pancreatic cancer cells and that a Src inhibitor (herbimycin A) inhibits the growth of said cells, in vitro (pg 503, final paragraph). Therefore, it would have been obvious to modify the general method of treating cancers with the Src inhibitor 4-(2-cholor-5-methoxyanilino)-6-methoxy-7-(*N*-methylpiperidin-4-ylmethoxy)quinazoline, as taught by Hennequin, et al, such that the method is used to treat pancreatic cancer as only the expected treatment of pancreatic cancer using an Src inhibitor would have been obtained, per the suggestion of Lutz, et al.

14. Furthermore, Bruns, et al., teach that an effective treatment in murine pancreatic cancer models is a combination treatment using gemcitabine and an epidermal growth factor receptor inhibitor (EGF-R) (Figure 2). Therefore, it also would have been obvious to further modify the anti-tumor treatment disclosed in Hennequin, et al., by combining the Src inhibitor with gemcitabine, per the teachings of Bruns et al, since using such a combination therapy to treat pancreatic cancer would be expected to be more beneficial than a single drug therapy.

Conclusion

15. No claims are allowed.

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Leu, et al. (Front. in Biosci., 01/2003), teach that Src and EGF-R are closely linked (Section 5.1). Maa, et al. (PNAS, 07/1995), teach that Src activation "synergistically increase[s] the oncogenic activity of EGFR" (Table 1).

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL ZAREK whose telephone number is (571)270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, PATRICK NOLAN can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Patrick J. Nolan/
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